

## Same-Single-Cell Analysis of Pacemaker-Specific Markers in Human Induced Pluripotent Stem Cell-Derived Cardiomyocyte Subtypes Classified by Electrophysiology.

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### Public Summary:

Markers that are specific to cardiac pacemaking cells can be used to identify and assess the maturity of human induced pluripotent stem cell (hiPSC)-derived pacemaker-like cardiomyocytes; however, the specificity of these markers has never been directly demonstrated because hiPSC-derived cardiomyocyte subtypes—pacemaker-, atrial-, and ventricular-like—can currently only be identified based on their electrical activity. For the first time, we directly assessed some proposed representative cardiac pacemaking cell-specific markers in the same-single hiPSC-derived cardiomyocytes that have been first identified as pacemaker-, atrial-, or ventricular-like subtypes by their electrical activity. Ion channel, HCN4, that is responsible for the pacemaking function and Isl1, a protein promoting pacemaking cardiomyocytes, were found to be more abundant in hiPSC-derived pacemaker-like cardiomyocytes, but the differences alone are insufficient in identifying hiPSC-derived pacemaker-like cardiomyocytes.

### Scientific Abstract:

Insights into the expression of pacemaker-specific markers in human induced pluripotent stem cell (hiPSC)-derived cardiomyocyte subtypes can facilitate the enrichment and track differentiation and maturation of hiPSC-derived pacemaker-like cardiomyocytes. To date, no study has directly assessed gene expression in each pacemaker-, atria-, and ventricular-like cardiomyocyte subtype derived from hiPSCs since currently the subtypes of these immature cardiomyocytes can only be identified by action potential profiles. Traditional acquisition of action potentials using patch-clamp recordings renders the cells unviable for subsequent analysis. We circumvented these issues by acquiring the action potential profile of a single cell optically followed by assessment of protein expression through immunostaining in that same cell. Our same-single-cell analysis for the first time revealed expression of proposed pacemaker-specific markers-hyperpolarization-activated cyclic nucleotide-modulated (HCN)4 channel and Islet (Isl)1-at the protein level in all three hiPSC-derived cardiomyocyte subtypes. HCN4 expression was found to be higher in pacemaker-like hiPSC-derived cardiomyocytes than atrial- and ventricular-like subtypes but its downregulation over time in all subtypes diminished the differences. Isl1 expression in pacemaker-like hiPSC-derived cardiomyocytes was initially not statistically different than the contractile subtypes but did become statistically higher than ventricular-like cells with time. Our observations suggest that although HCN4 and Isl1 are differentially expressed in hiPSC-derived pacemaker-like relative to ventricular-like cardiomyocytes, these markers alone are insufficient in identifying hiPSC-derived pacemaker-like cardiomyocytes. This article is protected by copyright. All rights reserved.

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